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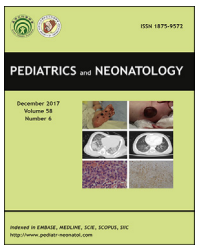

Original Article

Risk factors for poor outcomes of children with acute acalculous cholecystitis

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Key Words
acute acalculous cholecystitis (AAC);
children;
risk factor

Background: Acute acalculous cholecystitis (AAC) is generally considered to be a mild disease in children; however, if left untreated or treated without caution, AAC can lead to severe outcomes, such as death. The objectives of this study were to present the clinical features and identify the predictors of mortality in pediatric AAC.
Methods: Patients diagnosed with AAC between 2005 and 2012 were enrolled. AAC was defined by the presence of fever and an echo-proven thickened gallbladder wall exceeding 4 mm. A poor health outcome was defined as death. Further information related to the demographics, clinical manifestations, laboratory results, ultrasound findings, and pathogens present in the AAC patients was also collected. Predictors of mortality were identified by association analyses and confirmed by multivariate logistic regression.
Results: A total of 147 pediatric AAC patients (male/female = 1.01, mean age = 5.2 years) were included in this retrospective study. The most common clinical presentation was an elevated C-reactive protein level (84%) followed by hepatomegaly (80%) and anorexia (78%). AAC in children was associated with various diseases, including infectious diseases (70%), systemic diseases (13%), and malignancy (11%). Fourteen of the 147 (9.25%) patients died during the study period. The presences of thrombocytopenia, anemia, gallbladder sludge, hepatitis,

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and/or sepsis plus hepatitis were found to be the important predictors of AAC mortality.
Conclusions: The factors associated with AAC mortality were anemia, thrombocytopenia, gallbladder sludge, hepatitis, and sepsis plus hepatitis. These predictors are likely to help clinicians identify patients who are at a high risk of poor prognoses and make appropriate clinical decisions.

1. Introduction

Acute cholecystitis, inflammation of the gallbladder, is primarily caused by cholelithiasis in adults, and acute acalculous cholecystitis (AAC) causes only 2—15% of acute cholecystitis cases. However, among pediatric patients, AAC usually appears as a complication of other diseases, such as pneumonia, gastroenteritis, sepsis, and other systemic diseases.[1—5] AAC can also be found in patients with critical conditions including chemotherapy, bone marrow transplantation, immunosuppression, postsurgery symptoms, prolonged fasting, and major trauma.[6—10]

In adults, AAC can be treated with invasive procedures, such as cholecystectomy and percutaneous cholecystostomy. These harmless and low-risk surgeries should be arranged while the disease is mild to prevent severe complications and the recurrence of AAC.[11,12] Otherwise, approximately 40—100% of AAC patients may advance to gallbladder gangrene, gallbladder perforation, or multiorgan dysfunction. These advanced complications may eventually lead to death in 30% of patients.[12]

In adults, although AAC can be treated with surgical procedures, such as cholecystectomy and percutaneous cholecystostomy, for pediatric patients with AAC we primarily choose conservative treatments first. There are few studies of AAC operations in children. AAC can potentially lead to severe complications and cause death if left untreated; however, little is known about the predictors of these poor outcomes. Thus, the purposes of this study were to investigate the clinical manifestations, laboratory data, and pathogens related to AAC in addition to exploring their relationships with AAC-related death and identifying the important predictors to help clinicians make informed decisions.

2. Methods

The current study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taiwan. All pediatric patients who were admitted to Chang Gung Children's Hospital in Northern Taiwan because of AAC without surgery, trauma, or burn injury from January 2005 to December 2012 were reviewed. The criteria for enrollment included the following: (1) fever (from the medical notes), (2) thickening of the gallbladder wall exceeding 4 mm based on abdominal ultrasound (from imaging reports), and (3) clinical symptoms (at least one of the following: abdominal pain, vomiting, and jaundice). Individuals with congenital biliary tract abnormalities were excluded because of different bile juice flows and a higher incidence of cholecystitis.

The main outcomes of the current study were the indicators of poor prognoses, which were defined as death. The definition of AAC-related mortality was clarified as that occurring within 7 days after AAC onset. Information associated with the patients' clinical manifestations (such as fever duration, vital signs, and blood pressure), laboratory data (such as coagulation and blood culture test results), and the presence of pathogens (such as those identified by viral DNA analysis and bacterial culture) was collected retrospectively via the medical notes. Hepatitis was defined by an alanine aminotransferase (ALT) level of more than 200 U/L. The definition of sepsis was the presence of the clinical signs of fever combined with a positive blood culture finding. The analyzed abdominal ultrasound reports were those taken 3 days after fever onset from the eligible patients during hospitalization using a Siemens Acuson Antares Premium Edition (Siemens Medical Solutions USA, Inc., Mountain View, CA, USA) with a VFX 9-4 linear probe at frequencies of 2.5—6.15 Hz.

Clinical information and laboratory data related to disease severity were also collected. According to the newly developed severity grading system defined by the Tokyo Guidelines Revision Committee in 2013, also known as the TG13,[13] the disease severity was classified into three categories: mild, moderate, and severe. This classification is based on patients' symptoms (duration, local inflammation, and palpable right upper abdominal mass), laboratory data (leukocytosis, thrombocytopenia, and coagulopathy), and organ dysfunction (cardiovascular, neurological, renal, and hepatic dysfunction). Severe disease was defined as a condition in which the patient had developed organ dysfunction, and intensive care, including respiratory and circulatory management, was required. Moderate disease was defined by the presence of acute inflammation symptoms, including an elevated white blood cell count, a palpable tender mass over the right upper abdominal quadrant, a duration of symptoms exceeding 3 days, and marked local inflammation. Mild disease was defined by the presence of disease that failed to meet the criteria for moderate or severe disease.

Regarding the analyses, the patients' baseline characteristics and their clinical presentations were described using standard statistical analyses. To examine the associations between the indicators of poor outcome and the above-mentioned patient information, the chi-square test was used for the categorical variables, and the *t* test was used for the continuous variables. Finally, multivariate logistic regression with a stepwise procedure was used to explore the predictors of mortality. All analyses were performed using SAS version 9.2 statistical software (SAS 9.1

edn; SAS Institute Inc., Cary, NC, USA). Two-sided *p* values less than 0.05 were considered statistically significant.

3. Results

In total, 217 eligible pediatric patients were admitted to Chang Gung Children's Hospital over the 8-year study period. After reviewing the charts, 149 patients were found to meet the inclusion criteria (of having a history of fever). However, two of them had gallstones revealed on sonogram, which left a total of 147 AAC patients who were eligible for analyses.

The clinical features of the AAC patients are presented in Table 1. The median age of the 147 AAC patients was 4 years with a range of 9 days to 18 years. The median duration of fever was 4 days. Among these 147 AAC patients, 43 (29.25%) had been transferred to the intensive care unit (ICU) because of severe illness, and 14 (9.52%) of them unfortunately died. The laboratory results of the patients with AAC are also provided in Table 1. The most common abnormal laboratory sign was an elevated C-reactive protein (CRP) level (83.67%) followed by liver function impairment, which included abnormal aspartate aminotransferase (AST, 69.39%) and ALT (62.59%) levels and coagulopathy [international normalized ratio (INR) $>$ 2, 34.69%].

The clinical manifestations and ultrasound findings of the patients with AAC are listed in Table 2. As illustrated, the most common clinical manifestation was fever (100%), followed by anorexia (78.23%), jaundice (40.14%) and abdominal pain (36.05%). However, notably, the number of abdominal pain complaints might have been underestimated owing to poor expression of this symptom by pediatric patients. Apart from gallbladder wall thickening, the following image findings were most frequently observed: hepatomegaly (79.59%), ascites (44.90%), and splenomegaly (42.86%). Also, notably, up to 10.20% of the patients with AAC had sludge in the gallbladder that was related to bile stasis or influenced by a hemodynamic abnormality.

Several diseases and pathogens associated with AAC were observed in children (Table 3). The common infectious diseases associated with AAC were sepsis (14.98%), hepatitis (14.29%), and pneumonia (12.24%). The common viral pathogens found in the patients with AAC were Epstein–Barr virus (21.77%) and cytomegalovirus (CMV) (6.80%), and the common bacterial pathogens were *Streptococcus* (3.40%), *Escherichia coli* (2.72%), and *Staphylococcus* (2.04%).

The association analyses revealed that several clinical signs were associated with AAC death. The details can be

Table 1 Demographic and laboratory results of 147 pediatric AAC patients.

Demographics and outcome	
Age (y)	5.19 ± 4.45 (median age: 4 y)
Sex	M:/F = 74:73 (1.01)
Fever duration (d)	4.95 (median: 4 d, range: 1–30 d)
Intensive care	43 (29.25%)
Mortality	14 (9.52%)
Laboratory values*	
White blood cell count (1000/μL)	11.77 ± 8.22 (0.2–43.7)
Hemoglobin (g/dL)	11.14 ± 2.01 (5.6–14.8)
Platelet count (1000/μL)	184.02 ± 131.22 (4–574)
Prothrombin time (s)	17.14 ± 8.22 (10.5–62.2)
Activated partial thromboplastin time (s)	46.71 ± 18.73 (23.2–112.7)
International normalized ratio	1.76 ± 1.00 (1–15.5)
C-reactive protein (mg/L)	83.40 ± 94.19 (0.96–319.11)
Aspartate aminotransferase (U/L)	571.32 ± 1725.26 (11–15,892)
Alanine aminotransferase (U/L)	365.91 ± 713.87 (6–4807)
Blood urine nitrogen (mg/dL)	13.87 ± 14.82 (1.4–98)
Creatinine (mg/dL)	0.54 ± 0.55 (0.1–4.97)
Direct form bilirubin (mg/dL)	3.10 ± 4.63 (0.1–31)
Total bilirubin (mg/dL)	4.93 ± 6.48 (0.2–30.7)
r-glutamyl transpeptidase (U/L)	182.39 ± 201.65 (2–1211)
Alkaline phosphatase (U/L)	394.69 ± 540.76 (18–4192)
Albumin (g/dL)	3.18 ± 0.73 (1.69–4.7)

ACC = acute acalculous cholecystitis.
* The data are presented as mean ± standard deviation (minimum–maximum) unless otherwise indicated.

Table 2 Clinical manifestations and image findings (n = 147).

Clinical manifestations	
Fever	147 (100)
Anorexia	115 (78.23)
Jaundice	59 (40.14)
Abdominal pain	53 (36.05)
Vomiting	48 (32.65)
Diarrhea	37 (25.17)
Neurologic symptoms*	19 (12.93)
Abdominal distention	9 (6.12)
Cardiovascular dysfunction	6 (4.08)
Gastrointestinal bleeding	2 (1.36)
Imaging findings	
Gallbladder wall ≥ 4 mm	147 (100)
Hepatomegaly	117 (79.59)
Ascites	66 (44.90)
Splenomegaly	63 (42.86)
Gall sludge	15 (10.20)
Increased echogenicity of general hepatic area	15 (10.20)
Increased echogenicity of periportal area (biliary tree)	11 (7.48)
Enlarged intra-abdominal lymph node	4 (2.72)

The data are presented as n (%).
* Including headache, seizure, drowsiness, confusion, and dizziness.

Table 3 Clinical diseases and pathogens related to acute acalculous cholecystitis (AAC; $N = 147$).

Infectious diseases	103 (70.07)
Hepatitis	32 (21.77)
Sepsis (bacteremia and fungemia)	28 (19.05)
Pneumonia	18 (12.24)
Infectious mononucleosis	18 (12.24)
Acute gastroenteritis	13 (8.84)
Intra-abdominal infection	3 (2.04)
Urinary tract infection	2 (1.36)
Systemic diseases	20 (13.61)
Kawasaki disease	12 (8.17)
Systemic lupus erythematosus	4 (2.72)
Thalassemia	4 (2.72)
Malignancy	16 (10.88)
Hemophagocytic lymphohistiocytosis	7 (4.76)
Leukemia	5 (3.40)
Leukemia undergoing bone marrow transplantation	4 (2.72)
Other*	8 (5.44)
Virus	
Epstein—Barr virus	32 (21.77)
Cytomegalovirus	10 (6.80)
Mycoplasma	6 (4.08)
Influenza A virus	3 (2.04)
Other†	3 (2.04)
Bacteria	
Streptococcus species	5 (3.40)
Escherichia coli	4 (2.72)
Staphylococcus species	3 (2.04)
Pseudomonas species	3 (2.04)
Salmonella species	2 (1.36)
Klebsiella species	2 (1.36)
Acinetobacter baumannii	2 (1.36)
Haemophilus influenzae	2 (1.36)
Yeast (*Candida* species)	3 (2.04)
Parasite (*Plasmodium falciparum*)	1 (0.68)

* Including drug induced, malaria, and idiopathic etiology.
† Including hepatitis A virus, hepatitis B virus, and herpes simplex virus type I. The data are presented as *n* (%).

found in Table 4. Compared to the living patients, the patients who suffered mortality due to AAC seemed to be less likely to have anorexia and more likely to have anemia, a lower platelet count, a higher severity grading, impaired liver function [including more coagulopathy and prolonged activated partial thromboplastin time (APTT)], jaundice (elevated total and direct bilirubin levels), bile sludge, and sepsis plus hepatitis.

To further investigate the predictors of mortality in AAC, a multivariate logistic regression was conducted, and the results are presented in Table 5. As illustrated, factors such as anemia ($p = 0.031$), thrombocytopenia ($p = 0.046$), gallbladder sludge ($p = 0.017$), hepatitis ($p = 0.018$), and sepsis plus hepatitis ($p = 0.005$) were found to be significant predictors of mortality in AAC patients. After adjustments for other variables, patients with sepsis plus hepatitis were 114 times more likely to die from AAC than those without sepsis plus hepatitis.

4. Discussion

The current study aimed to identify the clinical signs (i.e., associated but not statistically significantly) and risk factors (i.e., statistically significantly associated) related to AAC death by examining all of the available clinical factors, which included the patients' clinical presentations, laboratory results, and complications. Many factors were found to be strongly associated with AAC death and could be considered to be signs in clinical practice (Tables 2 and 3). Some of these signs were further confirmed to be predictors (such as platelet abnormalities and gallbladder sludge) via regression analyses, and some of these signs were also in line with those presented in the literature (e.g., infectious diseases and severe illnesses[14—21]). In contrast, some of the signs, such as CRP, hepatomegaly, and anorexia are thought to be newly discovered and may become the predictors of poor outcome in terms of increasing severity scores in the future.

Although the sample size of this study is not extremely large ($n = 147$), it is sufficient to be considered representative of the general population based on the identical age and sex distributions. The average age of the study population was 5.2 years, and the median age was 4 years (Table 1). This distribution is in line with that of another published study conducted in Taiwan in 2011 (mean age = 5.8 years)[22] and slightly lower than those of other relevant studies (mean ages ranging from 7.8 to 9.0 years).[23,24] In terms of the sex ratio, no difference was observed between the two groups (male/female = 1.01:1). This sex distribution is also in line with those of relevant studies.[22—24]

AAC is related to many different diseases (Table 3). The associated disease itself may not result in death but may result in progression to mortality during the course of AAC. In our study, five patients with oncological diseases and one patient with systemic lupus erythematosus died. When the associated diseases and risk factors are coincident, mortality due to AAC increases. Therefore, we sought to be the first to evaluate the different factors that predict poor outcomes. Because different diseases are combined with AAC, we could identify some risk factors that could guide early intervention and prevent severe sequelae.

The main finding of the current study was the identification of the risk factors for pediatric AAC death. A small number of clinical signs were confirmed to be predictors in the regression analyses (Table 5). A lower hemoglobin level, a lower platelet count, gallbladder sludge, hepatitis, and sepsis plus hepatitis were found to be five of such predictors. The associations of these predictors with AAC death could be explained by the fact that all of them are good surrogate measures for liver function, inflammation, and infection.[8] When liver function deteriorates and/or infection occurs, the hemoglobin level and platelet count decrease, and the patient is more likely to experience poor and unfavorable health outcomes, such as death. Another important factor for predicting poor outcomes is bile sludge formation. The possible explanation is that the bile sludge leads to low bile flow and consequently causes severe inflammation that can lead to death. Finally, the key predictor that is worth mentioning is sepsis plus hepatitis.

Table 4 Relative risk factors for an association with death.

	Survival (n = 133)	Mortality (n = 14)	p
Clinical manifestation			
Fever > 3 d	77 (57.89)	8 (57.14)	0.957
Fever > 7 d	20 (15.04)	2 (14.29)	0.94
Anorexia	108 (81.20)	7 (50.00)	0.007
Vomiting	42 (31.58)	6 (42.86)	0.392
Abdominal pain	49 (36.84)	4 (28.57)	0.771
Severity			0.015
Mild	28 (21.05)	1 (7.14)	—
Moderate	55 (41.35)	2 (14.29)	—
Severe	50 (37.60)	11 (78.57)	—
Image			
Hepatomegaly	108 (81.20)	9 (64.29)	0.162
Splenomegaly	59 (44.36)	4 (28.57)	0.395
Ascites	58 (43.61)	8 (57.14)	0.333
Gallbladder sludge	13 (9.77)	4 (28.57)	0.038
Gallbladder wall 4–7 mm	105 (78.95)	11 (78.57)	0.684
Gallbladder wall > 7 mm	28 (21.05)	3 (21.43)	0.684
Echogenicity	22 (16.54)	4 (28.57)	0.262
Laboratory			
White blood cell (1000/μL)	12.23 ± 8.27	7.48 ± 6.53	0.039
Hemoglobin (g/dL)	11.31 ± 1.89	9.54 ± 2.52	0.002
Hematocrit (%)	34.26 ± 7.36	28.66 ± 8.04	0.008
Platelet (100/μL)	193.30 ± 132.30	96.50 ± 80.20	0.008
Prothrombin time (s)	16.21 ± 7.98	21.49 ± 8.26	0.034
Activated partial thromboplastin time (s)	44.27 ± 18.18	56.11 ± 18.45	0.034
International normalized ratio	1.72 ± 1.94	1.94 ± 0.74	0.679
C-reactive protein (mg/L)	82.07 ± 95.46	95.53 ± 83.98	0.613
Blood urine nitrogen (mg/dL)	12.96 ± 14.41	20.43 ± 16.78	0.102
Creatinine (mg/dL)	0.53 ± 0.50	0.63 ± 0.90	0.556
Aspartate aminotransferase (U/L)	563.60 ± 1801.80	639.40 ± 815.50	0.877
Alanine aminotransferase (U/L)	370.20 ± 743.80	331.40 ± 414.60	0.849
Direct form bilirubin (mg/dL)	2.38 ± 4.22	7.80 ± 4.60	<0.001
Total bilirubin (mg/dL)	3.57 ± 4.57	14.42 ± 9.61	<0.001
r-glutamyl transpeptidase (U/l)	193.90 ± 213.80	122.50 ± 108.80	0.309
Alkaline phosphatase (U/L)	330.30 ± 258.90	716.90 ± 1179.80	0.023
Albumin (g/dL)	3.25 ± 0.72	2.81 ± 0.71	0.038
Related diseases			
Sepsis	21 (15.79)	7 (50)	1.000
Hepatitis	26 (19.55)	6 (42.86)	0.427
Sepsis plus hepatitis	2 (1.50)	3 (21.43)	0.040
Systemic lupus erythematosus	4 (3.01)	1 (7.14)	0.312
Streptococcus infection	5 (3.76)	0 (0)	0.984

The data are presented as n (%) or mean ± the standard deviation.

Table 5 Multivariate logistic analysis of association with death.

	Multivariate analysis		
	Coefficient	p	OR (95% CI)
Hemoglobin	−0.37	0.031	0.69 (0.49–0.97)
Platelet count	−0.01	0.046	0.99 (0.98–1.00)
Gallbladder sludge	−1.01	0.017	0.13 (0.03–0.69)
Hepatitis	−1.09	0.018	0.11 (0.02–0.69)
Sepsis plus hepatitis	−1.62	0.005	0.04 (0.01–0.38)

CI = confidence interval; OR = odds ratio.

Because of this deadly inflammatory situation, patients with sepsis are prone to death (114 times more likely to die). These findings are in line with those reported in the relevant literature.[25,26]

Some predictors were found to lead to a worsening of the disease course without leading to death, for example, *Streptococcus* infection. Having a *Streptococcus* infection increased the risk of requiring ICU care without increasing the risk of death. A possible explanation for this finding is that although *Streptococcus* infection can cause sepsis and can introduce severe bacterial toxicity that could consequently lead to ICU care, it can be cured with antibiotic treatment, which prevents the worst health outcome, i.e.,

death. Age is another example. Similar to *Streptococcus* infection, a younger age could also increase the risk of requiring ICU care but not the risk of death. Unlike *Streptococcus* infection, a possible explanation for this finding is that age might not be associated with AAC severity. However, the effects of the illness on the appearance of younger patients might increase the chance of receiving ICU care for precautionary reasons.

There are a small number of signs that were expected to be predictors that could not be proven in the current study. The first are the white blood cell count and the CRP level. Both are strongly associated with infection or inflammation, similar to a low platelet count, but these signs appeared to have no associations with AAC death in this study. First, these findings can possibly be explained by the skewed laboratory results that were caused by unusual cases, such as patients receiving systemic lupus erythematosus (SLE) treatment, patients receiving chemotherapy for leukemia, and patients with a history of bone marrow transplantation. The second set of expected but unproven predictors are those associated with liver function, i.e., AST, ALT, bilirubin, PT, APTT, and INR. Although associations with poor outcomes were observed (Table 4), the predictive powers could not be confirmed (Table 5) primarily because these pieces of information were not incorporated into the regression analyses owing to the considerable numbers of missing values that could not be retrieved retrospectively. Incorporating this information would have compromised the numbers of patients available for the analyses and thus might have introduced bias.

Notably, there is another important sign that we did not incorporate into our current regression analyses, i.e., the TG13 severity score.[13] This score was strongly associated with AAC death (Table 4) and increased the chance of mortality ($p < 0.001$, data not shown). Although the results are promising, they must be interpreted with caution, primarily because we only examined AAC patients in inpatient settings. The lack of outpatient cases might have caused an underestimation of the number of low severity cases and a consequent overestimation or underestimation of the predictive power of the severity grade.

Although several important findings were obtained in this study, it is also subject to three limitations. First, information related to the length of hospitalization was not available primarily because of difficulties in retrieval and the determination of the date of diagnosis, especially among those with severe underlying diseases. Therefore, the statistical analyses of the clinical and economic influences of AAC could not be assessed. Second, according to the current clinical practices of the study hospital, regular follow-up abdominal sonograms were not arranged for all patients, and thus the resolution times for AAC could not be examined. Therefore, recovery time, which is one potential indicator of poor outcome, could not be investigated. Finally, several important pieces of information were left unexamined because of considerable numbers of missing values owing to the retrospective nature of the study. To complete this investigation and strengthen the results, a prospective study design involving more patients is desired.

AAC is broadly considered to be a mild disease among pediatric patients and is often neglected by clinicians. However, our study demonstrated that AAC can lead to severe health outcomes, including death, if not treated with caution. Additionally, in this study, we identified novel signs (such as CRP, hepatomegaly, and anorexia) and confirmed important risk factors (such as anemia, thrombocytopenia, bile sludge formation, hepatitis, and sepsis plus hepatitis) of AAC mortality. These signs and predictors are expected to support clinicians in making informed clinical decisions regarding patients who require intensive monitoring and/or interventions to reduce the possibility of severe health outcomes of AAC.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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